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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/914,883 | 01/22/2002 | Carlota Vinals Y De Bassols | BC45224 | 6044 |

20462 7590 01/24/2005

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

| EXAMINER | |
|---|---|
| YAEN, CHRISTOPHER H | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/914,883 | Y DE BASSOLS, CARLOTA VINALS | |
| | Examiner | Art Unit | |
| | Christopher H Yaen | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-45* is/are pending in the application.

4a) Of the above claim(s) *20 and 24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/02,3/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibits A and B*.

## DETAILED ACTION

**Re: Vinals-Bassols**
**Priority Date: 28 February 2000**

### *Election/Restrictions*

1. Applicant's election of group I (claims 17-19 and 21-23, specifically drawn to SEQ ID No: 2) in the reply filed on 10/25/2004 is acknowledged. Applicant argues that the separation of the inventions into the different groups is discretionary, but failed to provide any substantial arguments as to why the inventions should be regroup into a single invention. Therefore, as indicated in the prior office action (mailed 9/20/2004) the special technical feature linking the invention does not contribute over the prior art and therefore unity of invention is still lacking. Moreover, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 17-45 are pending, claims 20, and 24-45 are withdrawn as being drawn to non-elected invention(s).

3. Claims 17-19 and 21-23 are examined on the merits.

### *Information Disclosure Statement*

4. The Information Disclosure Statements filed 1/11/2002 and 3/15/2004 are acknowledged and considered. Signed copies of the IDSs are attached hereto.

### *Claim Objections*

5. Claims 17-19 are objected to because of the following informalities: claims recite terms that are drawn to non-elected inventions (i.e. claims recite SEQ ID No: 4). Appropriate correction is required.

***Claim Rejections - 35 USC § 112, 2nd paragraph***

6. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 18-19 and 21-23 are also rejected because these claims depend on base claim 17.

Specifically, claim 17 recites the phrase "which can include an adjuvant or a suitable carrier coupled to the polypeptide", it is unclear as to whether these elements (i.e. adjuvants or carriers) are part of the invention. Moreover, it is unclear if these elements are required for the function of eliciting an immune response. Appropriate correction or clarification is required.

***Claim Rejections - 35 USC § 112, 1st paragraph***

7. Claims 17-18 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth an amino acid sequence that consists of or comprises SEQ ID No: 2 and therefore the written description in this case is not commensurate in scope to the claims that read on variants, fragments, immunogenic fragments, or homologues of SEQ ID No: 2.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites ( page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of variant proteins encoded by allelic variant genes defined. With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the variants, fragments, and or homologues encompassed and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai*

*Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

The specification teaches (pages 3-4) that variants, fragments, immunogenic fragments and or homologues can encompass a genus of peptide sequences with the stated biological properties. However, the written description only reasonably conveys the peptide CASB616 (SEQ ID NO: 2). The instant disclosure of a single species of a peptide fails to adequately describe the scope of the claimed genus (any peptide sequence that is a variant, homologue or fragment), which encompasses a substantial variety of peptide sequences. A description of a genus of peptide variants, fragments, or homologues may be achieved by means of a recitation of a representative number of such sequences, defined by structure, falling within the scope of the genus. However, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of peptides sequences that would distinguish the claimed peptide sequences from other sequences that do not have the claimed biological properties. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one specific peptide is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are

clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only an isolated CASB616 polypeptide having an amino acid sequence of SEQ ID NO. 2 meets the written description provision of 35 USC 112, first paragraph.

***Claim Rejections - 35 USC § 101***

8. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility.

The current claims are drawn to an isolated polypeptide comprising a member selected from (a) an amino acid sequence that is at least 90% identical to SEQ ID No: 2; (b) an immunogenic fragment that is at least 90% identical to that of SEQ ID No: 2; and (c) an immunogenic fragment that is at least 90% identical to SEQ ID No: 2 that has no more than 5 single amino acid substitutions, deletions, or additions. Subsequent

claims limit or narrow the percent identity to SEQ ID No: 2 or limit the number of single amino acid substitutions, deletions, or additions.

**Credible Utility**

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The specification cites, as utilities for the CASB616 protein (SEQ ID No: 2), that the polypeptides are useful as treatments for cancer or autoimmune disease (see page 1, line 5) and in the diagnosis of tumor cells (see page 2, line 24). These utilities are credible.

Upon identification of a credible utility, the next issue is whether there are any well established utilities for the CASB616 protein (SEQ ID No: 2). A review of the specification and of the prior art finds no well established utilities for the use of the unknown protein termed CASB616 (SEQ ID No: 2), whose enzymatic or other biological function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the CASB616 protein (SEQ ID No: 2) which are identified in either the specification or in the prior art.

**Substantial Utility**

Here, the evidence in the specification provides that the nucleic acid (mRNA) that encodes the polypeptide of CASB616 is over-expressed in malignant colon cells (see

page 31). However, the specification fails to show that this over-expression in mRNA levels is directly correlative to over-expression in protein levels, nor has the specification taught that over-expression of the mRNA is indicative of any specific malignancies or involvement in autoimmune diseases. Moreover, one of skill in the art cannot extrapolate from the findings provided in the specification (such as on page 31), although drawn to the mRNA analysis, how the instantly claimed protein can be used in the detection of cancer or in autoimmune diseases, based only on the finding of mRNA over-expression in colon tissue samples. Even if there was a differential expression between normal and malignant colon tissue samples, the specification has not taught one of skill in the art that the claimed CASB616 protein is in fact expressed or over-expressed.

There is an abundance of art that teaches that the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M et al, 1995, Pediatric Res, 37 (6): 681-686). Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine

decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be over-expressed in CHO cells following exposure to radiation, without any concomitant over-expression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus in the instant case, one of skill in the art would not be able to predict if the CASB616 protein (SEQ ID No:2) or polypeptides that are 90-95% identical to SEQ ID No: 2 is in fact translated into a polypeptide expression product, or even if translated, whether they are over-expressed.

This situation is also analogous to example 4 of the Utility Guidelines, where a protein was disclosed by reference to a SEQ ID number and methods of making the

protein, but fails to disclose any chemical, physical, or biological properties for the protein other than the sequence, was found to lack utility. In the current case, the CASB616 protein (SEQ ID No: 2), lacks any substantial utility whatsoever and therefore any variant, fragment or homologue thereof would also lack a substantial utility. The specification does not even show that the protein is endogenously expressed in tissues as a protein, (the specification however does provide prophetic embodiments of expressing the protein recombinantly, see pages 34-35). So this case is similar to the uncharacterized protein of Example 4, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for CASB616. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

**Specific Utility**

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this CASB616 protein (SEQ ID No: 2) or any variant, fragment or homologue thereof. The protein, itself, has not been associated with any disease, any condition, or any other specific feature. There is no association of the protein with cancer or with any other disease, such as autoimmune disorders/diseases. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be

diagnosed". Here, the over-expression of the mRNA in cancerous colon tissue gives no specific utility for the protein or any variant, fragment or homologue thereof because the protein or any variant, fragment or homologue thereof has not been shown to be useful diagnostically, and it does not provide any evidence indicating a possible therapeutic use and simply represents a protein which may be expressed in a tissue. Until some function or some activity of the protein is identified, the protein or any variant, fragment or homologue thereof has no use. Therefore, there is no specific utility for the CASB616 protein or any variant, fragment or homologue thereof until a specific biological function or activity is identified.

With regard to the utility analysis, the current situation directly tracks that of examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

Given the teachings of unpredictability associated with protein expression and the lack of endogenous protein expression data of CASB616 in the specification, one of skill in the art cannot with any certainty correlate the teachings of the instant specification with any specific disease treatment or diagnosis, such as cancer or autoimmune diseases. Because the specification has only provided an expression profile of the CASB616 mRNA and has not taught how the instantly claimed protein functions, what its cellular role is, and what specific or substantial use the claimed polypeptide would have, utility is lacking. As such, the specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide and fragments thereof. Because the claimed invention is not

supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claims 17-19 and 21-23 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Pawson *et al* (WO 97/14966-A1). Claims are drawn to a isolated polypeptide comprising a member selected from (a) an amino acid sequence that is at least 90% identical to SEQ ID No: 2; (b) an immunogenic fragment that is at least 90% identical to that of SEQ ID No: 2; and (c) an immunogenic fragment that is at least 90% identical to SEQ ID No: 2 that has no more than 5 single amino acid substitutions, deletions, or additions. Claim 18 limits the percent identity of SEQ ID No: 2 to 95%, claim 19 limits the polypeptide as having the sequence of SEQ ID No: 2, claims 21-22 limit the claims to having no more than two single or a one single amino acid substitution, deletion, or either, respectively, and claim 23 limits the immunogenic

fragment to that which matches the aligned sequence. For the purposes of this rejection, the term "has" in claim 19 is interpreted as being open and is read to the extent that the term means "containing" a sequence of SEQ ID No: 2. Furthermore, because of the indefiniteness of claim 17, which recites "which can include an adjuvant or a suitable carrier", for the purposes of this rejection, the claim can be interpreted as either having or NOT having adjuvants or carriers.

Pawson *et al* teach a sequence (also known as SEQ ID No: 2, herein SEQ ID No: 2*) that has at least 98.9% identity to that of SEQ ID No: 2 (see attached Exhibit A). Pawson *et al* also teach fragments of SEQ ID No: 2' (see page 5, lines 12-18). Because the office does not have to ability to determine if the fragments taught by Pawson *et al* are indeed immunogenic, in the absence of evidence to the contrary, the fragments are immunogenic fragments. Further, because the sequence taught by Pawson *et al* is 98.9% identical to SEQ ID No: 2 it necessarily fulfills the limitation of at least 95% identical to that of SEQ ID No: 2. Moreover, Pawson *et al* also disclose fragments that are at least 20 contiguous amino acids from SEQ ID No: 2* (see page 5, lines 12-18) and therefore falls within the scope of both "no more than two" or " no more than one" single amino acid substitution, deletion, or addition, because no amino acid is either substituted, deleted or added to the fragment. And finally, because SEQ ID No: 2 is 98.9% identical to that of SEQ ID No: 2' and because fragments have been disclosed by Pawson *et al*, it would also "match the aligned sequences" as claimed.

If claim 17 is interpreted as having carriers, Pawson *et al* teaches that pharmaceutical carriers can be included in the invention (see page 5, lines 12-18).

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 17-19 and 21-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Pawson *et al* (US Patent 6,218,356). Claims are drawn to a isolated polypeptide comprising a member selected from (a) an amino acid sequence that is at least 90% identical to SEQ ID No: 2; (b) an immunogenic fragment that is at least 90% identical to that of SEQ ID No: 2; and (c) an immunogenic fragment that is at least 90% identical to SEQ ID No: 2 that has no more than 5 single amino acid substitutions, deletions, or additions. Claim 18 limits the percent identity of SEQ ID No: 2 to 95%, claim 19 limits the polypeptide as having the sequence of SEQ ID No: 2, claims 21-22 limit the claims to having no more than two single or a one single amino acid substitution, deletion, or either, respectively, and claim 23 limits the immunogenic fragment to that which matches the aligned sequence. For the purposes of this rejection, the term "has" in claim 19 is interpreted as being open and is read to the extent that the term means "containing" a sequence of SEQ ID No: 2. Furthermore, because of the indefiniteness of claim 17, which recites "which can include an adjuvant

or a suitable carrier", for the purposes of this rejection, the claim can be interpreted as either having or NOT having adjuvants or carriers.

Pawson *et al* teach a sequence (also known as SEQ ID No: 2, herein SEQ ID No: 2*) that has at least 98.9% identity to that of SEQ ID No: 2 (see attached Exhibit B). Pawson *et al* also teach fragments of SEQ ID No: 2* (see col. 7, lines 41-52). Because the office does not have to ability to determine if the fragments taught by Pawson *et al* are indeed immunogenic, in the absence of evidence to the contrary, the fragments are immunogenic fragments. Further, because the sequence taught by Pawson *et al* is 98.9% identical to SEQ ID No: 2 it necessarily fulfills the limitation of at least 95% identical to that of SEQ ID No: 2. Moreover, Pawson *et al* also disclose fragments that are at least 20 contiguous amino acids from SEQ ID No: 2* (see col. 7, line 41) and therefore falls within the scope of both "no more than two" or " no more than one" single amino acid substitution, deletion, or addition, because no amino acid is either substituted, deleted or added to the fragment. And finally, because SEQ ID No: 2 is 98.9% identical to that of SEQ ID No: 2* and because fragments have been disclosed by Pawson *et al*, it would also "match the aligned sequences" as claimed.

If claim 17 is interpreted as having carriers, Pawson *et al* teaches that pharmaceutical carriers can be included in the invention (see col. 29, lines 23-26).

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
January 10, 2005

883-2.rag

Exhibit A



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Qy        720 VIQLVGMLRGIAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPT 779
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Qy        900 INLPLLDRTIPDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRLGVT 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||:|:|
Db        901 INLPLLDRTIPDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRVGLT 959

Qy        960 LAGHQKKILNSIQVMRAQMNQIQSVEV 986
              ||||||||||||||||||||||||||
Db        961 LAGHQKKILNSIQVMRAQMNQIQSVEV 987
```

RESULT 6
AAW26366
ID  AAW26366 standard; protein; 994 AA.
XX
AC  AAW26366;
XX
DT  02-DEC-1997  (first entry)
XX
DE  Mouse Nuk tyrosine kinase.
XX
KW  Nuk tyrosine kinase; Eph receptor tyrosine kinase; signal transduction;
KW  axonogenesis; neurodegenerative disease; Alzheimer's disease;
KW  Parkinson's disease; Huntington's disease; multiple sclerosis;
KW  amyotrophic lateral sclerosis; Wernicke's disease; nerve damage; trauma;
KW  ischaemia; stroke.
XX
OS  Mus musculus.
XX

| FH | Key | Location/Qualifiers |
|---|---|---|
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| FT | | /label= Sig_peptide |
| FT | Protein | 27. .994 |
| FT | | /label= Mat_protein |
| FT | Domain | 27. .548 |
| FT | | /label= Extracellular_domain |
| FT | Region | 330. .420 |
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| FT | Region | 444. .534 |
| FT | | /label= FNIII |
| FT | | /note= "fibronectin type III repeat" |
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| FT | Domain | 575. .994 |
| FT | | /label= Cytoplasmic_domain |
| FT | Region | 623. .888 |
| FT | | /label= Tyrosine-kinase_region |

XX
PN  WO9714966-A1.
XX
PD  24-APR-1997.
XX
PF  10-OCT-1996;  96WO-CA000679.
XX
PR  13-OCT-1995;  95US-0005518P.
XX
PA  (MOUN ) MOUNT SINAI HOSPITAL CORP.
XX
PI  Pawson A,  Henkemeyer M;
XX
DR  WPI; 1997-245245/22.
DR  N-PSDB; AAT84528.

Exhibit A (cont.)

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XX
PT   Activation of ligand regulatory pathways by Eph subfamily receptor
PT   tyrosine kinases - for stimulating or inhibiting axonogenesis, useful for
PT   treatment of e.g. neuro:degenerative diseases such as Alzheimer's or
PT   Parkinson's diseases.
XX
PS   Disclosure; Fig 3; 55pp; English.
XX
CC   Murine Nuk tyrosine kinase is an Eph subfamily receptor tyrosine kinase
CC   that is essential for formation of the medial tract of the anterior
CC   commissure of the brain, and which appears to play a role in the
CC   formation of the habenular interpeduncle tract. Its amino acid sequence
CC   was deduced from cDNA clones (see AAT84528) isolated from an embryo cDNA
CC   library. The extracellular domain of Nuk was shown to be sufficient for
CC   formation of the medial tract. Eph subfamily receptor tyrosine kinases
CC   (e.g. the Nuk extracellular domain) can be used in claimed methods to:
CC   activate a ligand regulatory pathway in a cell; identify substances able
CC   to bind a ligand for an Eph subfamily receptor tyrosine kinase; and to
CC   affect neuronal development or regeneration, especially the stimulation
CC   or inhibition of axonogenesis, in a mammal. Activation of the ligand
CC   regulatory pathway results in downstream activation of a series of
CC   regulatory pathways in cells that control gene expression, cell division,
CC   cytoskeletal architecture, cell metabolism, cell migration and cell-cell
CC   interactions. Substances which activate the ligand regulatory pathway may
CC   be used for stimulating or inhibiting neuronal development regeneration
CC   and axonal migration associated with neurodegenerative disease e.g.
CC   Alzheimer's, Parkinson's or Huntington's diseases, multiple sclerosis,
CC   amyotrophic lateral sclerosis, deficiency diseases such as Wernicke's
CC   disease, peripheral nerve damage, trauma and ischaemia resulting from
CC   stroke
XX
SQ   Sequence 994 AA;

  Query Match           98.9%;  Score 5130;  DB 2;  Length 994;
  Best Local Similarity 99.5%;  Pred. No. 0;
  Matches  972;  Conservative    4;  Mismatches    1;  Indels    0;  Gaps    0;

Qy         10 LLLLPLLAAVEETLMDSTTATAELGWMVHPPSGWEEVSGYDENMNTIRTYQVCNVFESSQ 69
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         18 LLLLPLLAAVEETLMDSTTATAELGWMVHPPSGWEEVSGYDENMNTIRTYQVCNVFESSQ 77

Qy         70 NNWLRTKFIRRRGAHRIHVEMKFSVRDCSSIPSVPGSCKETFNLYYYEADFDSATKTFPN 129
              ||||||||||||||||||||||||||||||||||||||||||||||||| |||||||
Db         78 NNWLRTKFIRRRGAHRIHVEMKFSVRDCSSIPSVPGSCKETFNLYYYEADFDLATKTFPN 137

Qy        130 WMENPWVKVDTIAADESFSQVDLGGRVMKINTEVRSFGPVSRSGFYLAFQDYGGCMSLIA 189
              ||||||||||||||||||||||||||||||||||||||||||||:||||||||||||||||
Db        138 WMENPWVKVDTIAADESFSQVDLGGRVMKINTEVRSFGPVSRNGFYLAFQDYGGCMSLIA 197

Qy        190 VRVFYRKCPRIIQNGAIFQETLSGAESTSLVAARGSCIANAEEVDVPIKLYCNGDGEWLV 249
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        198 VRVFYRKCPRIIQNGAIFQETLSGAESTSLVAARGSCIANAEEVDVPIKLYCNGDGEWLV 257

Qy        250 PIGRCMCKAGFEAVENGTVCRGCPSGTFKANQGDEACTHCPINSRTTSEGATNCVCRNGY 309
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        258 PIGRCMCKAGFEAVENGTVCRGCPSGTFKANQGDEACTHCPINSRTTSEGATNCVCRNGY 317

Qy        310 YRADLDPLDMPCTTIPSAPQAVISSVNETSLMLEWTPPRDSGGREDLVYNIICKSCGSGR 369
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        318 YRADLDPLDMPCTTIPSAPQAVISSVNETSLMLEWTPPRDSGGREDLVYNIICKSCGSGR 377

Qy        370 GACTRCGDNVQYAPRQLGLTEPRIYISDLLAHTQYTFEIQAVNGVTDQSPFSPQFASVNI 429
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        378 GACTRCGDNVQYAPRQLGLTEPRIYISDLLAHTQYTFEIQAVNGVTDQSPFSPQFASVNI 437

Qy        430 TTNQAAPSAVSIMHQVSRTVDSITLSWSQPDQPNGVILDYELQYYEKELSEYNATAIKSP 489
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        438 TTNQAAPSAVSIMHQVSRTVDSITLSWSQPDQPNGVILDYELQYYEKELSEYNATAIKSP 497

Qy        490 TNTVTVQGLKAGAIYVFQVRARTVAGYGRYSGKMYFQTMTEAEYQTSIQEKLPLIIGSSA 549
              ||||||||||||||||||||||||||||||||||||||||||||:|||||:||||
Db        498 TNTVTVQGLKAGAIYVFQVRARTVAGYGRYSGKMYFQTMTEAEYQTSIKEKLPLIVGSSA 557

Qy        550 AGLVFLIAVVVIAIVCNRRGFERADSEYTDKLQHYTSGHMTPGMKIYIDPFTYEDPNEAV 609
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        558 AGLVFLIAVVVIAIVCNRRGFERADSEYTDKLQHYTSGHMTPGMKIYIDPFTYEDPNEAV 617

Qy        610 REFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLPGKREIFVAIKTLKSGYTEKQRRDFLS 669
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        618 REFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLPGKREIFVAIKTLKSGYTEKQRRDFLS 677

Qy        670 EASIMGQFDHPNVIHLEGVVTKSTPVMIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRG 729
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        678 EASIMGQFDHPNVIHLEGVVTKSTPVMIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRG 737

Qy        730 IAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPTYTSALGGKIP 789
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        738 IAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPTYTSALGGKIP 797

Qy        790 IRWTAPEAIQYRKFTSASDVWSYGIVMWEVMSYGERPYWDMTNQDVINAIEQDYRLPPPM 849
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        798 IRWTAPEAIQYRKFTSASDVWSYGIVMWEVMSYGERPYWDMTNQDVINAIEQDYRLPPPM 857

Qy        850 DCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSGINLPLLDRTI 909
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        858 DCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSGINLPLLDRTI 917

Qy        910 PDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRLGVTLAGHQKKILN 969
              ||||||||||||||||||||||||||||||||||||||||||||||:||||||||||||||
Db        918 PDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRVGVTLAGHQKKILN 977

Qy        970 SIQVMRAQMNQIQSVEV 986
              |||||||||||||||||
Db        978 SIQVMRAQMNQIQSVEV 994
```

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RESULT 7
AAU01907
ID   AAU01907 standard; protein; 994 AA.
XX
AC   AAU01907;
XX
DT   29-AUG-2001  (first entry)
XX
DE   Murine neural kinase (Nuk) polypeptide.
XX
KW   Neural kinase; Nuk; receptor tyrosine kinase; axonal migration; stroke;
KW   nerve fibre; cell-cell interaction; axonogenesis; neuronal development;
KW   regeneration; neurodegenerative disorder; Alzheimer's disease; ischaemia;
KW   Parkinson's disease; Huntington's disease; demyelinating disease;
KW   multiple sclerosis; amyotrophic lateral sclerosis; deficiency disease;
KW   Wernicke's disease; nutritional polyneuropathy; multistem degeneration;
KW   progressive supranuclear palsy; Shy Drager's syndrome; mouse;
KW   olivo ponto cerebellar atrophy; peripheral nerve damage.
XX
OS   Mus musculus.
XX
FH   Key             Location/Qualifiers
FT   Peptide         1. .26
FT                   /note= "Signal peptide"
FT   Domain          26. .544
FT                   /note= "Extracellular domain, preferably residues 26-544"
FT   Protein         27. .994
FT                   /note= "Mature murine neural kinase"
FT   Domain          52. .119
FT                   /note= "Ig-like domain"
FT   Region          239. .268
FT                   /note= "Ig-like Nuk repeat"
FT   Region          330. .420
FT                   /note= "Fibronectin type III repeat"
FT   Region          444. .534
FT                   /note= "Fibronectin type III repeat"
FT   Domain          549. .574
FT                   /note= "Hydrophobic transmembrane domain"
FT   Binding-site    600. .618
FT                   /note= "SH2 domain binding site"
```

Exhibit B

RESULT 1
US-08-542-635-2
; Sequence 2, Application US/08542635
; Patent No. 6218356
; GENERAL INFORMATION:
; APPLICANT: Pawson, Anthony
; APPLICANT: Henkemeyer, Mark
; APPLICANT: Letwin, Kenneth
; TITLE OF INVENTION: NOVEL NEURAL RECEPTOR
; TITLE OF INVENTION: TYROSINE KINASE
; NUMBER OF SEQUENCES: 2
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Bereskin & Parr
; STREET: 40 King Street West, Box 401
; CITY: Toronto
; STATE: Ontario
; COUNTRY: Canada
; ZIP: M5H 3Y2
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.25
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/542,635
; FILING DATE:
; CLASSIFICATION: 800
; ATTORNEY/AGENT INFORMATION:
; NAME: McDiarmid, Shona S.
; REGISTRATION NUMBER: 38,798
; REFERENCE/DOCKET NUMBER: 3153-162
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (416) 364-7311
; TELEFAX: (416) 361-1398
; TELEX: 06-23115
; INFORMATION FOR SEQ ID NO: 2:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 994 amino acids
; TYPE: amino acid
; STRANDEDNESS: single
; TOPOLOGY: linear
; MOLECULE TYPE: protein
; ORIGINAL SOURCE:
; ORGANISM: Mus musculus
; DEVELOPMENTAL STAGE: Embryo
; IMMEDIATE SOURCE:
; LIBRARY: lamda gt10 cDNA library
; CLONE: Combined pNukRACE A2 and K2 and cDNA clones
; POSITION IN GENOME:
; CHROMOSOME/SEGMENT: Distal end of chromosome 4
; MAP POSITION: near the ahd-1 mutation
US-08-542-635-2

Query Match 98.9%; Score 5130; DB 3; Length 994;
Best Local Similarity 99.5%; Pred. No. 0;
Matches 972; Conservative 4; Mismatches 1; Indels 0; Gaps 0;

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Qy          10 LLLLPLLAAVEETLMDSTTATAELGWMVHPPSGWEEVSGYDENMNTIRTYQVCNVFESSQ 69
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          18 LLLLPLLAAVEETLMDSTTATAELGWMVHPPSGWEEVSGYDENMNTIRTYQVCNVFESSQ 77

Qy          70 NNWLRTKFIRRRGAHRIHVEMKFSVRDCSSIPSVPGSCKETFNLYYYEADFDSATKTFPN 129
               ||||||||||||||||||||||||||||||||||||||||||||||||||| |||||||||
Db          78 NNWLRTKFIRRRGAHRIHVEMKFSVRDCSSIPSVPGSCKETFNLYYYEADFDLATKTFPN 137

Qy         130 WMENPWVKVDTIAADESFSQVDLGGRVMKINTEVRSFGPVSRSGFYLAFQDYGGCMSLIA 189
               ||||||||||||||||||||||||||||||||||||:||||||||||||||||||||||||
Db         138 WMENPWVKVDTIAADESFSQVDLGGRVMKINTEVRSFGPVSRNGFYLAFQDYGGCMSLIA 197

Qy         190 VRVFYRKCPRIIQNGAIFQETLSGAESTSLVAARGSCIANAEEVDVPIKLYCNGDGEWLV 249
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         198 VRVFYRKCPRIIQNGAIFQETLSGAESTSLVAARGSCIANAEEVDVPIKLYCNGDGEWLV 257

Qy         250 PIGRCMCKAGFEAVENGTVCRGCPSGTFKANQGDEACTHCPINSRTTSEGATNCVCRNGY 309
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         258 PIGRCMCKAGFEAVENGTVCRGCPSGTFKANQGDEACTHCPINSRTTSEGATNCVCRNGY 317

Qy         310 YRADLDPLDMPCTTIPSAPQAVISSVNETSLMLEWTPPRDSGGREDLVYNIICKSCGSGR 369
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         318 YRADLDPLDMPCTTIPSAPQAVISSVNETSLMLEWTPPRDSGGREDLVYNIICKSCGSGR 377

Qy         370 GACTRCGDNVQYAPRQLGLTEPRIYISDLLAHTQYTFEIQAVNGVTDQSPFSPQFASVNI 429
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         378 GACTRCGDNVQYAPRQLGLTEPRIYISDLLAHTQYTFEIQAVNGVTDQSPFSPQFASVNI 437

Qy         430 TTNQAAPSAVSIMHQVSRTVDSITLSWSQPDQPNGVILDYELQYYEKELSEYNATAIKSP 489
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         438 TTNQAAPSAVSIMHQVSRTVDSITLSWSQPDQPNGVILDYELQYYEKELSEYNATAIKSP 497
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Exhibit B (cont.)

Mon Aug 30 08:48:58 2004

us-09-914-88

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Qy      490 TNTVTVQGLKAGAIYVFQVRARTVAGYGRYSGKMYFQTMTEAEYQTSIQEKLPLIIGSSA 549
Db      498 TNTVTVQGLKAGAIYVFQVRARTVAGYGRYSGKMYFQTMTEAEYQTSIKEKLPLIVGSSA 557
Qy      550 AGLVFLIAVVVIAIVCNRRGFERADSEYTDKLQHYTSGHMTPGMKIYIDPFTYEDPNEAV 609
Db      558 AGLVFLIAVVVIAIVCNRRGFERADSEYTDKLQHYTSGHMTPGMKIYIDPFTYEDPNEAV 617
Qy      610 REFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLPGKREIFVAIKTLKSGYTEKQRRDFLS 669
Db      618 REFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLPGKREIFVAIKTLKSGYTEKQRRDFLS 677
Qy      670 EASIMGQFDHPNVIHLEGVVTKSTPVMIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRG 729
Db      678 EASIMGQFDHPNVIHLEGVVTKSTPVMIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRG 737
Qy      730 IAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPTYTSALGGKIP 789
Db      738 IAAGMKYLADMNYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPTYTSALGGKIP 797
Qy      790 IRWTAPEAIQYRKFTSASDVWSYGIVMWEVMSYGERPYWDMTNQDVINAIEQDYRLPPPM 849
Db      798 IRWTAPEAIQYRKFTSASDVWSYGIVMWEVMSYGERPYWDMTNQDVINAIEQDYRLPPPM 857
Qy      850 DCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSGINLPLLDRTI 909
Db      858 DCPSALHQLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSGINLPLLDRTI 917
Qy      910 PDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRLGVTLAGHQKKILN 969
Db      918 PDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRVGVTLAGHQKKILN 977
Qy      970 SIQVMRAQMNQIQSVEV 986
Db      978 SIQVMRAQMNQIQSVEV 994
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